Evidence for Impaired Glucose Effectiveness in Cirrhotic Patients After Liver Transplantation

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To evaluate the impact of acute and chronic liver disease and single immunosuppression (cyclosporine A [CSA] or FK506) on insulin sensitivity and glucose effectiveness in liver-grafted patients, we performed a frequently sampled intravenous glucose tolerance test (FSIGTT) in nondiabetic patients after orthotopic liver transplantation (OLT) with acute liver failure ([ALF] group, n = 9, with CSA therapy), in patients after OLT with chronic liver disease (CSA group, n = 8; FK506 group, n = 8), and in 9 healthy control subjects. Insulin sensitivity and glucose effectiveness were determined by analyzing glucose and insulin data from the FSIGTT with Bergman's minimal model technique for glucose. The intravenous glucose tolerance index ([K_G] ie, the slope of the regression of the logarithm of blood glucose concentration) was not different between the ALF group (2.17 ± 0.16 min^{-1}) and controls (2.29 ± 0.13 min^{-1}), but was lower ($P < .05$) in both groups with chronic liver disease (CSA group, 1.46 ± 0.1; FK506 group, 1.61 ± 0.11 min^{-1}) compared with the ALF group ($P < .05$). A positive relation for the K_G and glucose effectiveness was found in all liver-grafted patients and controls. Insulin sensitivity was not different between all liver-grafted patients and controls. The body mass index (BMI) was the overall determinant of insulin sensitivity in all groups. Single immunosuppressive therapy does not impair insulin sensitivity in liver-grafted patients. The lower glucose effectiveness in liver-grafted patients with chronic liver disease but not in patients after ALF points to a defect in the regulation of glucose-mediated glucose uptake in peripheral tissue.

GLUCOSE TOLERANCE after an oral or intravenous glucose load depends on the complex interaction between insulin secretion from β cells and the action of insulin to accelerate glucose disappearance and inhibit endogenous glucose production, ie, insulin sensitivity.[1] An additional factor contributing to glucose tolerance is glucose effectiveness, defined as the ability of glucose per se, independent of increased insulin, to normalize the glucose concentration through actions on glucose production and utilization.[2] Glucose effectiveness has more importance when insulin sensitivity decreases, and is considered as a compensatory mechanism in the regulation of glucose homeostasis.[3] In contrast to insulin sensitivity, which is predominantly influenced by the body mass index (BMI), waist circumference, maximal aerobic capacity, and life-style factors such as smoking and alcohol consumption, glucose-mediated glucose uptake is independent of such factors but strongly influenced by physical activity,[4] undernutrition, and impaired protein energy malnutrition.[5] Glucose-mediated glucose uptake can be pharmacologically influenced by either elevating[6] or blocking[7] glucose uptake in muscle tissue.

Insulin resistance is a characteristic feature in nearly all patients with acute[8] and chronic[9] liver disease. However, glucose effectiveness appears to be impaired only in cirrhotic patients with frank diabetes mellitus.[10,11] Defects of both insulin- and glucose-mediated glucose uptake in diabetic cirrhotic patients have been detected in peripheral muscle tissue.[10-12] Insulin resistance in cirrhosis is thought to be caused by an impairment of insulin-dependent glucose transport systems and intracellular key enzymes of glucose utilization.[12,13] The pathomechanism of glucose resistance in cirrhotic patients with frank diabetes mellitus is not clearly understood, but appears to be related to changes in glucose transport systems in muscle tissue.[10] However, contradictory results were reported by Marchesini et al,[14] who demonstrated with the minimal-model approach that the ability of glucose per se to promote glucose utilization is reduced about 45% in cirrhotic but nondiabetic patients. A decrease in glucose effectiveness explained 65% of the variance of glucose disappearance in these cirrhotic patients. They also found a positive relation between glucose effectiveness ($r = .839$, $P < .01$) and the urinary creatinine ratio, which is an indirect measure of muscle mass, therefore indicating that a reduction of this factor appears to be related to a decrease of muscle mass in cirrhotic patients.[14] Summarizing these findings, glucose effectiveness is less sensitive to individual parameters such as body weight but more sensitive to muscle composition and changes of intracellular glucose pathways in muscle tissue.

The question now arises as to whether end-stage liver disease characterized by muscle wasting and acute liver failure (ALF) without such clinical symptoms have any impact on factors of glucose tolerance such as insulin sensitivity and glucose effectiveness in liver-grafted patients. Although insulin sensitivity has been evaluated in a large number of studies in liver-grafted patients, the effect of immunosuppression on glucose effectiveness has never been investigated. Impairment of glucose homeostasis associated with insulin resistance is commonly diagnosed after transplantation,[15-17] and seems related to long-term therapy with immunosuppressive agents.[16,18-20] Cyclosporine A (CSA) and FK506 appear to have similar diabetogenic activity[21]; however, in the long-term, FK506 may

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have a less detrimental effect on glucose metabolism because its higher immunosuppressive potency allows a lower total steroid requirement.[22]

To clearly define the impact of CSA and FK506 monotherapy on insulin sensitivity and glucose effectiveness, we selected only liver-grafted patients with chronic liver disease from our recent study[23] who had no family history of diabetes mellitus, no virus-induced liver disease, no insulin requirement in the perioperative and postoperative periods after orthotopic liver transplantation (OLT), no rejection episode after OLT, and stable liver function over the years. We also evaluated the question of whether insulin sensitivity and glucose effectiveness are different in liver-grafted patients who are exposed to long-term malnutrition caused by chronic liver disease compared with liver-grafted patients after ALF. For this purpose, we selected only patients with end-stage liver disease caused by primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), or alcoholism, which are characterized by an increased breakdown of adipose tissue and muscle.[24] To answer these questions, we performed a frequently sampled intravenous glucose tolerance test (FSIGTT) interpreted with the Bergman minimal model for glucose.[25] This technique is a powerful noninvasive tool to investigate both factors of glucose tolerance, ie, insulin sensitivity and glucose effectiveness, in healthy,[1] diabetic,[6] and cirrhotic[11,14] subjects.

SUBJECTS AND METHODS

Patient Assessment

Sixteen cirrhotic patients after OLT (CSA group, n = 8; FK506 group, n = 8) from our recent study,[23] 9 liver-transplanted patients after ALF (with CSA therapy), and 9 healthy control subjects with normal glucose tolerance on an oral glucose tolerance test according to World Health Organization criteria underwent a FSIGTT. All patients with chronic liver disease had histologically proven liver cirrhosis before transplantation (Child C), and some had the characteristic signs of malnutrition and were in a severely catabolic stage (CSA, n = 6; FK506, n = 4). Only cirrhotic patients with non–virus-induced liver disease (CSA: alcoholic liver disease, n = 4; PBC, n = 5; FK506: alcoholic liver disease, n = 5; PBC, n = 3; PSC, n = 1) underwent these tests. The cause of ALF finally leading to transplantation could not be identified in the ALF group. Virus screening tests after liver transplantation were also negative.

None of the liver-transplanted patients had diabetes mellitus before transplantation. Exclusion criteria were perioperative or postoperative insulin treatment, cardiovascular, renal, and infectious diseases, alcoholism and drug abuse, estrogen therapy, and a positive family history of diabetes mellitus. Graft function and liver enzymes were in the normal range. The immunosuppressive perioperative and postoperative regimens in both groups were standardized as previously described.[23] Antihypertensive medication (α-blockers) was used equally in CSA and FK506 groups and in the ALF group. None of these patients were taking β-blockers or diuretics. The medium interval after OLT was 53 ± 4 months in the CSA group, 48 ± 7 months in the FK506 group, and 38 ± 4 months in the ALF group, respectively.

The transplanted patients with ALF were compared with nondiabetic controls matched for glucose tolerance, body weight, age, and sex from our metabolic research unit (Table 1). It must be mentioned that the controls and patients of this study had similar physical activity as assessed by full working capacity and regular physical training. All subjects undergoing these tests received detailed instructions for recording food intake for 3 days, with a recommendation for the last food intake to be at 8 PM in the evening. The caloric content of the food was not to exceed 2,000 kcal/d. Written consent was obtained from all subjects before study.

FSIGTT

After an overnight fast, a polyethylene catheter was inserted in the antecubital vein for blood sampling. Another one was used in the contralateral arm for intravenous glucose administration. Baseline samples for glucose and insulin were obtained at −15, −10, −5, and 0 minutes. Glucose (300 mg/kg body weight, 50% solution) was administered intravenously within 2 minutes, and blood samples were collected as previously described.[6]

Analytical Procedures

The plasma glucose concentration was measured in duplicate by the glucose oxidase method on a glucose analyzer (Beckman Clinical System 700; Beckman Instruments, Fullerton, CA). Blood samples for plasma insulin were immediately centrifuged at 4°C and stored at 20°C until analysis. To avoid any cross-reactivity with proinsulin, insulin concentrations were measured by a microparticle-enzyme immunoassay (MEIA Insulin, IMX System, Abbott; Weisbaden, Germany). The within-assay coefficient of variation (CV) was 5.3%, and total assay variation was 6.2%. CSA and FK506 serum levels were analyzed as previously described.[23] Before the FSIGTT, glucagon (Glucagon RIA; Serono Diagnostics, Freiburg, Germany), cortisol (Enzymun-Test; Boehringer, Mannheim, Germany), and serum growth hormone (STH, HGH MAIAclone; Biochem Immuno Systems, Freiburg, Germany) levels were measured. Cholesterol and triglycerides were determined enzymatically using available commercially kits (CHOL SYS3 and TG SYS3; Boehringer).

Glucose Disappearance Rate and Kinetic Models

Intravenous glucose tolerance as assessed by the glucose disappearance rate (K_G) was calculated to compare the model-derived parameters

Table 1. Clinical Characteristics and Counterregulatory Hormones in Controls and Liver-Grafted Patients

Characteristic	Controls (n = 9)	ALF Group (n = 9)	CSA Group (n = 8)	FK506 Group (n = 8)
Age (yr)	42 ± 5	37 ± 4	42 ± 1	44 ± 4
Gender (female/male)	4/5	4/5	4/4	4/4
Waist to hip ratio	0.81 ± 0.05	0.83 ± 0.02	0.79 ± 0.03	0.83 ± 0.04
Fasting glucose (mmol/L)	4.16 ± 0.12	4.11 ± 0.13	3.92 ± 0.21	4.24 ± 0.26
Fasting insulin (pmol/L)	58.77 ± 11.59	74.98 ± 7.56	65.92 ± 5.41	80.52 ± 6.05
Fasting glucagon (ng/L)	99 ± 21	92 ± 16	108 ± 29	119 ± 11
Fasting STH (μg/L)	2.3 ± 0.1	2.1 ± 0.8	3.1 ± 0.5	2.9 ± 0.2
Fasting cortisol (ng/dL)	10.6 ± 1.6	9.6 ± 2.6	10.2 ± 2.2	11.2 ± 2.1
Total cholesterol (mg/dL)	203 ± 23	196 ± 29	242 ± 14	218 ± 12
Triglycerides (mg/dL)	206 ± 15	186 ± 9	208 ± 26	191 ± 12

Abbreviation: STH, somatotropic hormone.

as the slope of the regression of the logarithm of blood glucose concentration against time between 10 and 50 minutes after intravenous glucose injection, as previously described.[6] FSIGTT data analysis was based on the Bergman minimal model of glucose disappearance.[25] Glucose and insulin profiles were analyzed using SAAM II software version 1.0.2 (University of Washington, Seattle, WA). The glucose measurement error was determined to be constant fractional standard deviation (FSD) equal to 2% of the measured value.

The minimal model of glucose disappearance[25] is used to fit the plasma glucose time course while assuming that the time course of insulin is known, and in the process providing 2 metabolic indices that measure glucose effectiveness (S_G) and insulin sensitivity (S_I). It must be appreciated that these parameters are composite parameters, ie, they measure the effect of glucose and insulin, respectively, both to enhance glucose disappearance and to inhibit endogenous glucose release (ie, they cannot segregate the contribution of the liver and peripheral tissues to plasma glucose kinetics). To mitigate the consequences of the single-compartment approximation of glucose kinetics on which the minimal model relies, glucose data points up to 8 minutes were not used during the fitting process. Basal endtest glucose and insulin concentrations, necessary for the minimal model identification, were calculated as the mean of the last 3 data points. The precision of parameter estimates was expressed as the FSD, ie, the ratio between the standard deviation of the estimate and the estimated value, expressed as a percent.

Statistical Analysis

Data are expressed as the mean ± SE. To evaluate differences between the control group and the patient groups, 1-way ANOVA was used, or 1-way ANOVA on ranks if normality was not found. Correlations were determined using linear regression, with a P value less than .05 considered significant.

RESULTS

Physical characteristics and laboratory data for the liver-transplanted patients and controls are shown in Table 1. CSA serum concentrations in liver-grafted patients with cirrhosis and patients after ALF were not different (306 ± 27 *v* 315 ± 35 ng/mL, respectively). The FK506 serum level was about 5.6 ± 0.82 ng/mL.

FSIGTT profiles for glucose and insulin in the liver-grafted groups and controls are charted in Figs 1, 2, and 3. Fasting glucose and insulin concentrations were not different between controls and patients. No differences were found for the glucose and insulin time courses during the FSIGTT between the control group and ALF group (Fig 1). Comparing glucose profiles of liver-grafted patients with cirrhosis versus the ALF group, glucose levels reached higher peaks immediately after glucose administration in the liver-grafted groups with chronic liver disease, which were then followed by a weaker decay. The increase in insulin levels after glucose-loading and the subsequent decrease were similar in all liver-grafted groups with cirrhosis and ALF (Figs 2 and 3).

Modeling analysis of FSIGTT data revealed no significant differences in insulin sensitivity among all liver-grafted patients (CV 2% to 16%) and controls (CV 2% to 11%; Tables 2 and 3). Insulin sensitivity was negatively related to the BMI in all groups (controls, $r = -.72$; CSA group, $r = -.76$; FK506 group, $r = -.78$; ALF group, $r = -.68$; $P < .05$ for all). Fasting glucose in all patients was also negatively related to insulin sensitivity (controls, $r = -.83$, $P < .01$; CSA group, $r = -.72$; FK506 group, $r = -.78$; ALF group, $r = -.75$;

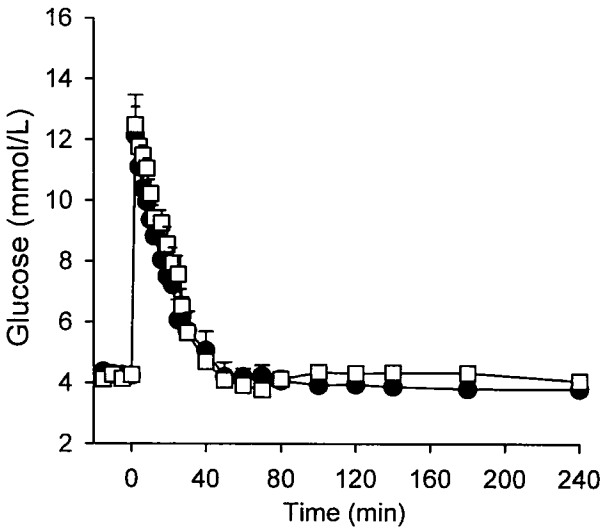

Fig 1. Glucose and insulin profiles after the FSIGTT in controls (●) and liver-grafted patients with ALF (□).

$P < .05$). A large variation in glucose effectiveness (CV 3% to 10%) was found in both grafted groups with liver cirrhosis, from 1.12 to 2.57 × $10^{-2} \cdot min^{-1}$. Glucose effectiveness was significantly lower in liver-grafted patients with cirrhosis compared with ALF patients (Table 3). The calculated intravenous glucose disposal rate (K_G) was significantly lower in liver-grafted patients with chronic liver disease ($P < .05$) compared with patients with ALF. Intravenous glucose tolerance in the patients and controls was strongly influenced by glucose effectiveness (CSA, $r = .85, p < .01$; FK506, $r = .93, P < .001$; ALF, $r = .90$, $P < .001$; controls, $r = .92$, $P < .001$) (Table 3).

DISCUSSION

Diminished insulin sensitivity probably caused by the combination of reduced hepatic insulin degradation and subsequent

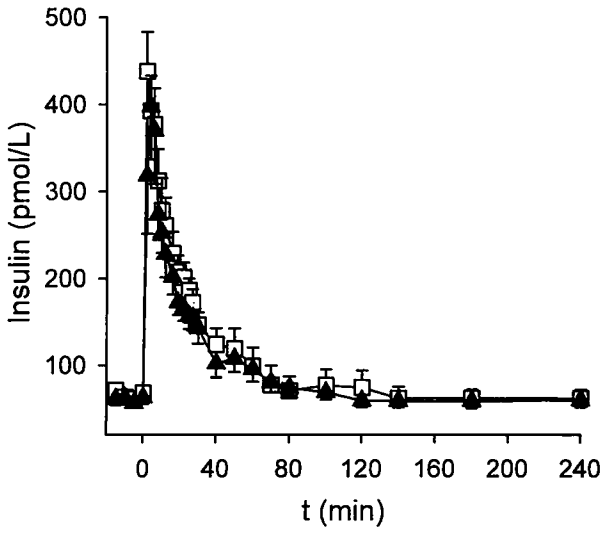

Fig 2. Glucose and insulin profiles after the FSIGTT in liver-grafted patients with ALF (□) and patients with chronic liver disease and CSA therapy (▲).

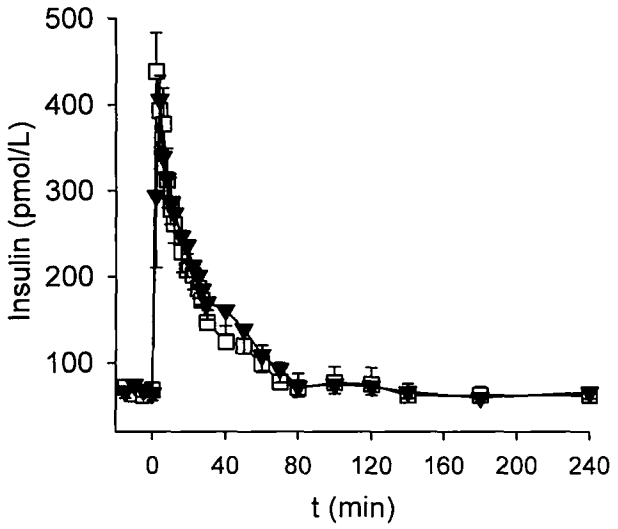

Fig 3. Glucose and insulin profiles after the FSIGTT in liver-grafted patients with ALF (□) and patients with chronic liver disease and FK506 therapy (▼).

hyperinsulinemia[26] is commonly found in nearly all patients with liver cirrhosis.[9] In this regard, we can assume on the basis of our present data that liver transplantation is capable of correcting this characteristic abnormality of glucose metabolism in liver cirrhosis. The negative relation of insulin sensitivity with fasting glucose in our liver-grafted patients may reflect an intact regulation of hepatic glucose production in the fasting state in patients after liver transplantation, as reported recently.[27] Since physical activity, liver function, and body composition as assessed by a normal BMI and waist to hip ratio were not different in our liver-grafted patients and controls, we suggest that body composition and physical activity were normalized after liver transplantation in our patients, confirming other findings.[28-30] Our results show that body mass is the overall determinant of insulin sensitivity in liver-grafted patients, as commonly known for healthy subjects.[31] Furthermore, single immunosuppressive therapy, ie, CSA and FK506, does not impair insulin sensitivity in liver-grafted patients when given over a longer time. Considering the normal lipid parameters in our liver-grafted patients under single immunosuppression, we can support the finding by Stegall et al[32] that concomitant steroid therapy seems to be the predominant cause for pathological changes of these parameters in these patients.

Glucose effectiveness in patients with cirrhosis varied greatly, from low values as in diabetic cirrhotic patients ($1.46 \pm 0.18 \times 10^{-2} \cdot min^{-1}$, from Kruszynska et al[11]) to normal values as in controls. Since glucose effectiveness did not differ between controls and liver-grafted patients after ALF, it is likely that chronic liver disease per se may be one explanation for the large variability of glucose effectiveness in these patients, and not the immunosuppressive therapy. Further reasons for the individual variability in glucose effectiveness may be related to the mechanisms involved in glucose uptake and its subsequent intracellular utilization, ie, differences in glucose transporter types and activity, and individual variability in oxidative and nonoxidative pathway function.[33] Using hyperglycemic/isoglycemic clamp techniques, Perseghin et al[29] reported recently that hyperglycemia alone was able to suppress endogenous glucose production and stimulate glucose uptake in patients after OLT, and therefore, their results are in contrast to our findings. They also showed that oxidative and nonoxidative glucose-mediated glucose metabolism was normal. The differences between these results and ours might be explained first by the different methods applied and second by the different

Table 2. BMI, K_G, and the Model-Derived Parameters S_I and S_G in Healthy Control Subjects and Liver-Grafted Patients With ALF

Subject No.	BMI (kg/m²)	K_G (min^{-1})	S_I ($10^{-4} \cdot min^{-1} \cdot \mu U/mL$)	S_G ($10^{-2} \cdot min^{-1}$)
Controls				
1	18.3	2.29	8.36	2.44
2	25.0	1.93	3.85	2.32
3	23.1	1.86	9.70	2.12
4	22.1	2.23	7.21	2.59
5	27.2	2.80	1.39	2.83
6	20.0	2.65	8.63	3.10
7	24.1	1.94	3.73	2.08
8	24.6	2.56	9.33	2.96
9	26.6	2.43	1.17	2.69
Mean ± SE	23.4 ± 1.0	2.29 ± 0.11	5.93 ± 1.14	2.52 ± 0.12
ALF patients				
1	21.78	1.68	7.41	2.13
2	30.78	2.43	1.65	2.70
3	23.40	2.60	5.55	3.33
4	23.82	2.54	5.27	2.93
5	22.13	1.34	6.90	1.92
6	21.99	2.86	4.06	3.74
7	27.55	2.12	2.31	2.77
8	20.59	1.86	3.31	2.29
9	23.56	2.06	5.32	2.78
Mean ± SE	23.96 ± 1.08	2.17 ± 0.16	4.64 ± 0.66	2.61 ± 0.16

Table 3. BMI, CSA and FK506, K_G, and the Model-Derived Parameters S_I and S_G in Liver-Grafted Patients With Chronic Liver Disease

Patient No.	BMI (kg/m²)	K_G (min^{-1})	S_I ($10^{-4} \cdot min^{-1} \cdot \mu U/mL$)	S_G ($10^{-2} \cdot min^{-1}$)
CSA group				
1	20.4	1.55	7.01	2.02
2	21.3	2.09	6.24	2.43
3	20.3	1.24	4.87	1.19
4	20.0	1.26	6.27	1.12
5	26.7	1.37	4.23	1.66
6	22.5	1.25	7.67	1.48
7	21.9	1.34	6.80	1.81
8	27.7	1.54	1.22	1.93
Mean ± SE	22.6 ± 1.1	1.46 ± 0.10*	5.54 ± 0.73	1.71 ± 0.16*
FK506 group				
1	22.1	1.56	6.99	1.83
2	20.7	1.34	7.15	1.65
3	25.9	1.69	1.52	2.16
4	23.5	1.86	1.34	2.57
5	25.6	1.27	1.71	1.38
6	27.3	1.25	1.36	1.26
7	23.3	1.72	5.49	1.93
8	21.8	2.15	3.22	2.44
Mean ± SE	23.7 ± 0.8	1.61 ± 0.11*	3.60 ± 0.90	1.90 ± 0.17*

*$P < .05$ *v* ALF group.

selection of patients for these examinations. However, both steady-state (clamp) and dynamic (FSIGTT) measurements of S_G yield comparable values,[34] since glucose-stimulated glucose uptake is the dominant pathway for peripheral glucose disposal for both techniques.[34] The studies by Perseghin et al[29] were performed in cirrhotic patients with hepatocellular carcinoma. Although we did not quantify the clinical and nutritional state of our patients before transplantation, most of them were characterized by muscle wasting, which is commonly found in patients with end-stage liver disease caused by PSC, PBC, or alcoholism.[24,30,35] Since changes in glucose effectiveness correlate strongly with the loss of muscle mass in liver cirrhosis,[14] we assume that although body composition and physical activity are normalized after liver transplantation, a defect may persist in muscle tissue in our patients with chronic liver disease, probably due to a defect in the acute translocation of glucose transporter after an acute glucose elevation or in intracellular glucose utilization.[36,37]

The calculated intravenous glucose tolerance (K_G) of all subjects undergoing these tests was above the diabetic range ($>1.0\ min^{-1}$, Cerasi and Luft[38]), but was lower in liver-grafted groups with cirrhosis. Intravenous glucose tolerance is predominantly regulated by glucose effectiveness and first-phase insulin secretion in healthy[1,33] and nondiabetic cirrhotic[11] subjects. The first-phase insulin responsiveness of β cells to glucose determines the range of intravenous glucose disposal rates for an individual[1] by inhibiting hepatic glucose production, but it has no impact on peripheral glucose disposal.[39] Using the minimal modeling technique for C-peptide,[40] we showed recently that first-phase insulin secretion was not different in these cirrhotic patients after OLT compared with healthy subjects. Therefore, the lower glucose tolerance during the FSIGTT can be attributed to the lower glucose effectiveness only. This is also supported by the finding in our healthy subjects, as well as our liver-grafted patients, that glucose effectiveness and K_G are closely related, as reported by others.[3,11,33] The early decline of glucose that occurs immediately after glucose injection is mainly caused by glucose effectiveness, which acts over the mass action itself independently of insulin increases.[33,34] Thus, the higher increments in glucose levels immediately after a glucose load in our liver-grafted patients with chronic liver disease appear to be caused by the lower glucose effectiveness in these patients.

In summary, the present study provides evidence that glucose-mediated glucose uptake appears impaired in liver-grafted patients with chronic liver disease. Although the reason that liver-grafted patients with chronic liver disease have decreased glucose effectiveness is not known at present, their individual abnormality of glucose effectiveness may contribute to the higher incidence of diabetes mellitus in these patients.[15,16] Further studies on the regulation of glucose homeostasis in patients before and after liver transplantation are required to clarify our results.

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